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10/715,417	11/19/2003	Eivind Per Thor Straten	60820.000004	5850

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
12/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,417	STRATEN ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12,13,18,19,21,23-25,29-31,33-36 and 38-49* is/are pending in the application.

4a) Of the above claim(s) *12,13,18,19,29-31 and 41-49* is/are withdrawn from consideration.

5)☒ Claim(s) *1 & 25* is/are allowed.

6)☒ Claim(s) *21,23,24,33-36 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/23/09 & 9/25/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 8/17/09 is acknowledged and has been entered.

2. The terminal disclaimer filed on 8/17/09 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on application umber 10/354,090 has been reviewed and is accepted. The terminal disclaimer has been recorded.

3. The terminal disclaimer filed on 8/17/09 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on application umber 10/543,755 has been reviewed and is accepted. The terminal disclaimer has been recorded.

4. Applicant is reminded of Applicant's election with traverse of Group I and species of SEQ ID NO: 14 as the native human survivin peptide sequence and SEQ ID NO: 36 as the modified survivin peptide in Applicant's response filed 12/21/06. The Examiner notes that the instant claims no longer recite either SEQ ID NO.

Claims 1, 21, 23-25, 33-36 and 38-40 are currently being examined.

5. Applicant's amendment filed 8/17/09 has overcome the prior rejection of record of claims 1, 21, 23-25, 33-36 and 38-40 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (written description).

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 38-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This new ground of rejection is necessitated by Applicant's amendment filed 8/17/09.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the

inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed invention, a complex of a peptide according to claim 1 and a Class I HLA molecule or a fragment of such molecule, including wherein the complex is monomeric or multimeric.

The instant claims encompass a complex comprising any HLA class I molecule or fragment of such molecule and a MHC class I restricted epitope peptide derived from survivin, comprising SEQ ID NO: 5, wherein the epitope peptide has a C50 value, defined as the concentration of the peptide required for half-maximal binding to HLA-A2, which is at the most 20 uM, *i.e.,* the HLA molecule may not be HLA-A2.

Evidentiary reference Rammensee *et al* (Immunogenetics, 50: 213-219, 1999, IDS reference) teaches over 100 HLA class I alleles (see Table 3 on page 216).

The instant specification does not disclose a representative number of species of peptide comprising SEQ ID NO: 5 that bind to any other but HLA-A2, and hence does not disclose a representative number of species of claimed complex comprising any HLA class I molecule or fragment thereof with a peptide comprising SEQ ID NO: 5 (see for instance, Examples). The specification does not disclose which amino acid residues would be permissive for binding to which undisclosed hundreds of other HLA class I molecules.

Given these considerations, adequate written description has not been established.

8. Applicant's amendment filed 8/17/09 has overcome the prior rejection of record of claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 under 35 U.S.C. 112, first paragraph, scope of enablement.

9. Claims 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the isolated peptide recited in instant claim 1, does not reasonably provide enablement for an immunogenic composition comprising the isolated peptide recited in instant claim 1, wherein the composition is capable of eliciting an immune response against a cancer disease where survivin is expressed, including the cancer diseases recited in instant claim 34, nor wherein the composition elicits production in the recipient subject of effector T cells having a cytotoxic effect against the cancer cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This new ground of rejection is necessitated by Applicant's amendment filed 8/17/09.

The specification has not enabled the breadth of the claimed invention because the claims encompass an immunogenic composition comprising SEQ ID NO: 5 (which is a position 2 substituent analog peptide of survivin 96-104) which may not be capable of eliciting an immune response against a cancer disease where survivin is expressed and which may not elicit production of CTL having a cytotoxic effect against the cancer cells

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed invention can be made and/or used.

The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs)" ([0009]), and that "U.S. Pat. No. 6,245,523 discloses the isolation of purified survivin and it provides nucleic acid molecules that encode the survivin protein, and antibodies and other molecules that bind to survivin U.S. Pat. No. 6,245,523 also discloses anti-apoptotically active fragments of the survivin protein and variants hereof wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed survivin sequence. It is specifically disclosed that such peptides should contain key functional residues required for apoptosis, *i.e.,* Trp at position 67, Pro at position 73 and Cys at position 84" ([0011]). The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs). In a global gene expression analysis of about 4 million transcripts, survivin was identified as one of the top genes invariably up-regulated in many types of cancer but not in normal tissue (8)" [0009].

The specification further discloses that the peptides of the invention are derived from the known sequence of survivin, *e.g.,* the sequence disclosed in U.S. Pat. No. 6,245,523, and that the selection of peptides potentially having the ability to bind to a particular HLA molecule can be made by the alignment of known sequences that bind to a given particular HLA molecule to thereby reveal the predominance of a few related amino acids at particular positions in the peptides, *i.e.,* anchor residues ([0027]). The specification discloses "a simple approach to identifying peptides of the invention includes the following steps: selecting a particular HLA molecule, *e.g.* one occurring at a high rate in a given population, carrying out an alignment analysis as described above to identify "anchor residue motifs" in the survivin protein, isolating or constructing peptides of a suitable size that comprise one or more of the identified anchor residues and testing the resulting peptides for (i) capability to bind to the particular HLA molecule using the assembly assay as described herein, (ii) the capability of the peptides to elicit INF-.gamma.-producing cells in a PBL population of a cancer patient at a frequency of at least 1 per 10^4 PBLs as determined by an ELISPOT assay as described herein, and/or (iii) the capability of the peptides to detect *in situ* in a tumour tissue CTLs that are reactive with the epitope peptides being tested" ([0031]).

The specification discloses that some nonamer and decamer peptides that are subsequences of human survivin or substitution variants of said peptides can bind to selected HLA class I molecules (especially Table 4). The specification discloses that five stage IV melanoma patients were vaccinated with the modified HLA-A2 restricted sur1M2 peptide (SEQ ID NO: 5) loaded onto autologous dendritic cells, resulting in a strong T cell response to said peptide, and the detection of infiltration of survivin reactive cells into visceral and soft tissue metastases using *in situ* peptide/HLA-A2 multimer staining (page 44 at lines 4-11). The specification discloses that SEQ ID NO; 1, 4 and 5 bind to HLA-A2 with *C50* of 30, 1 and 1 uM, respectively, and that CTL or TIL from some CLL or melanoma patients could recognize or cross-react with complexes of SEQ ID NO: 5 and HLA-A2 (especially Table 1).

Thus, the specification discloses that SEQ ID NO: 5 binds with high affinity to HLA-A2, reacts with TIL or CTL from tumor-bearing patients, and can be loaded onto dendritic cells to produce a cell composition that can induce production of T cells that can home to soft tissue and visceral metastases. However, the specification does not disclose that a composition comprising the isolated peptide comprising SEQ ID NO: 5 is immunogenic.

Celis *et al* (Mol. Immunol. 1994. 31(18): 1423-1430, of record) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens. Ochoa-Garay *et al* (Mol. Immunol. 1997. 34(1): 273-281) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto page 280).

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768, of record) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (*e.g.,* by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis

further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Therapy. 1(3): 497-510, 2001, of record) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) teach that "The ELISPOT methodology represents a strong tool to monitor peptide-specific T-cell response. However, although it has been shown that ELISPOT reactivity in most cases correlates with the capacity to lyse the target cell, the formal proof for this notion can be given only directly" (page 5966 at column 2, lines 3-7).

The disclosed use of the immunogenic composition of the invention is to treat cancer ([0022]).

Therefore, because of the demonstrated unpredictability in the art of immunogenicity of peptide compositions and cancer immunotherapy, and in the absence of sufficient exemplification and guidance, one skilled in the art cannot make and/or use the claimed invention with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 8/17/09 on pages 11-14.

With regard to Applicant's arguments that pertain to the instant rejection, the following response applies.

Applicant argues that the MPEP states that data generated using *in vitro* assays or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process

so long as the data is reasonably correlated to the asserted utility. Applicant cites the Examples in the instant specification to support this position.

However, the Examples in the specification involve not an isolated peptide composition as is recited in the instant claims, but rather involve a dendritic cell composition wherein the peptide SEQ ID NO: 5 is pre-loaded onto the cells. The evidentiary references cited in this rejection establish that whether a peptide is immunogenic needs to be tested in assays that establish immunogenicity, that immunogenicity may not always be predicted based upon affinity of binding to a class I MHC molecule, that factors such as peptide hydrophobicity and stability can influence immunogenicity, as can CTL precursor frequency, and that compositions consisting of peptides are likely to be ineffective at inducing T cell immunity and/or high affinity CTL. The evidentiary references also establish unpredictability in the correlation of the ability of IFN-γ producing cells identified in ELISPOT assays with their ability to lyse target cells. Thus, the scope of the claims in the instant application is not reasonably commensurate with the scope of the enabling disclosure.

10. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim encompass a peptide that is capable of eliciting INF-gamma producing cells in a PBL population of a patient having a cancer disease, said INF-gamma producing cells having cytotoxic effect against survivin expressing cells of a cancer cell line, including a line selected from the group consisting of the melanoma cell line FM3. There is insufficient disclosure in the specification on such a cell line.

Claim 24 was previously rejected upon the ground set forth below in the prior Office Action of record with regard to the cell line FM3. (Applicant's response filed 8/17/09, providing the ATCC number of the cell line MCF-7, has overcome the said prior rejection with regard to the cell line MCF-7.)

The Examiner notes the US 20040176573 publication of the instant application discloses that MCF-7 is available from ATCC, *i.e.*, "[0127] Conventional [51Cr]-release assays for CTL-mediated cytotoxicity were carried out as described in (13). Target cells were autologous EBV-transformed B-cell lines, the HLA-A2 positive breast cancer cell line MCF-7 (available at ATCC), the HLA-A2 positive melanoma cell line FM3 (38), the HLA-A2 negative breast cancer cell line BT-20 (available from ATCC) and the HLA-A2 negative melanoma cell line FM45 (38). All cancer cell lines expressed survivin as examined by RT-PCR (data not shown)."

It is also noted by the Examiner that Applicant's amendment filed 9/24/07 (on page 24) as well as the said declaration of Dr. Andersen under 37 CFR 1.132 (at item #6 on page 3) states "[t]he cell line was originally described by Kirkin *et al* (Cancer Immunol. Immunother, 41: 71-81, 1995) [the aforementioned reference 38 disclosed at [0127] above] and is well recognized within the art." However, the cell line must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public as enunciated below.

The FM3 cell line is essential to the claimed invention. The reproduction of an identical cell line is an extremely unpredictable event. The cell line must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the cell line, and it is not apparent if the cell line is readily available to the public.

If a deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been made under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application is required.

If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(A) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(B) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(C) the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer;

(D) a viability statement in accordance with the provisions of 37 C.F.R. 1.807;

(E) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function in the manner described in the specification.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under 37 C.F.R. 1.132 is necessary to construct a chain of custody. Cell line .... was deposited after the time of filing. The declaration, executed by a person in a position to know, should identify the deposited cell line by its depository accession number, establish that the deposited cell line is the same as that described in the specification, and establish that the deposited plasmid was in Applicants possession at the time of filing. In re Lundak, 27 USPQ 90.

Biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

Therefore, because of the unpredictability in the art of making an identical cell line, and by extension a peptide that is capable of eliciting cells that have a cytotoxic effect against said cell lines, one skilled in the art cannot make and/or use the claimed invention with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant's said arguments are of record in the response filed 8/17/09 on pages 15-16.

Applicant has stated that the melanoma cell line FM3 is available to researchers from the ESTDAB database cell bank at a nominal cost structured to cover the costs incurred by ESTDAB in the preparation of the cell line order. Applicant has also submitted an entry from Wikipedia which lists the melanoma cell line FM3.

However, it appears that the deposit was not made under the provisions of the Budapest Treaty, and the certifications that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809 have not been made.

11. Applicant is reminded that the attempt to incorporate subject matter (the FM3 melanoma cell line) into this application by reference to Kirkin *et al* (Cancer Immunol. Immunother, 41: 71-81, 1995) at [0127] and [0272] of the US 20040176573 publication of the instant application is ineffective because the incorporation of *essential* material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the Applicant, or a practitioner representing the Applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter into the instant application by reference to a publication is improper because an application as filed must be complete in itself in order to comply with 35 USC 112. An application for a patent when filed may incorporate "essential material" by reference to (1) a US patent or (2) a US patent application publication, which patent or patent publication does not itself incorporate such essential material by reference. "Essential material" is defined as that which is necessary to (1) provide a written description of the claimed invention, and the manner and process of making and using it, in such full, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention, (2) describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 USC 112, or (3) describe the structure, material or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 USC 112. In any application which is to issue as a US patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the US or foreign countries or regional patent offices, (2) prior and concurrently filed, commonly owned US applications, or (3) non-patent publications. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Disclosure made by Applicant in the US 20040176573 publication of the instant specification is as follows:

"[0127] Conventional [51Cr]-release assays for CTL-mediated cytotoxicity were carried out as described in (13). Target cells were autologous EBV-transformed B-cell lines, the HLA-A2 positive breast cancer cell line MCF-7 (available at ATCC), the HLA-A2 positive melanoma cell line FM3 (38), the HLA-A2 negative breast cancer cell line BT-20 (available from ATCC) and the HLA-A2 negative melanoma cell line FM45 (38). All cancer cell lines expressed survivin as examined by RT-PCR (data not shown)", and

"[0272] 38. Kirkin, A. F., Reichert Petersen, T., Olsen, A. C., Li, L., Thor Straten, P., and Zeuthen, J. Generation of human-melanoma specific T lymphocyte clones defining novel cytolytic targets with panels of newly established melanoma cell lines. Cancer Immunol. Immunother., 41: 71-81, 1995."

The Examiner notes that although the words "incorporate" and "by reference" do not appear in the specification in this regard, "the melanoma cell line FM3" is recited in original claim 24, and [0127] discloses reference 38 (Kirkin *et al*) listed in the specification to be associated with FM3.

Applicant does not address this issue, however, Applicant has stated (in the response filed 8/17/09 on pages 15-17) that the melanoma cell line FM3 is available to researchers from the ESTDAB database cell bank at a nominal cost structured to cover the costs incurred by ESTDAB in the preparation of the cell line order. Applicant has also submitted an entry from Wikipedia which lists the melanoma cell line FM3.

However, the information provided by Applicant is in Applicant's response, rather than in the specification, and the attempt to incorporate essential material by reference to a non-patent literature document is ineffective as enunciated supra.

12. Applicant is reminded that the incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

13. Applicant's amendment filed 8/17/09 has overcome the prior rejection of record of claims 1, 21, 23, 25, 28, 33-36, 38-40 and 50 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 23, 24, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 24 was rejected upon the basis set forth below in the prior rejection of record. Applicant's amendment filed 8/17/09 has necessitated the following new rejection of claim 23, 34 and 35 upon the basis set forth below.

a. Claim 24 is indefinite in the recitation of "the breast cancer cell line MCF-7 and the melanoma cell line FM3" because their characteristics are not known. The use of "MCF-7 and FM3" as the sole means of identifying the claimed cell lines renders the claim indefinite because "MCF-7 and FM3" is merely a laboratory designation which does not clearly define the cell lines that the cells elicited by the claimed product have cytotoxicity against, since different laboratories may use the same laboratory designations to define completely distinct cell lines.

b. Claims 23 and 34 recite the limitation "wherein the cancer disease is selected from the group consisting of" the recited cancers at lines 1-4. There is insufficient antecedent basis for this limitation in the claim. Applicant has amended base claim 1 to delete reference to cancer disease.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record on pages 16-17 of the amendment filed 8/17/09.

However, in response to said arguments, claim 24 does not recited the ATCC number of cell line MCF-7 (*i.e.,* ATCC HTB-22), and it is not clear what "FM3" refers to because of the enablement rejection over claim 24 and the ineffective attempt to incorporate essential subject matter by reference to a non-patent literature document, both enunciated supra in this Office Action.

16. For the purpose of prior art rejections, the filing date of the instant claims 21, 23, 34-36 and 40 is deemed to be the filing date of the instant application, *i.e.,* 11/19/03, as the parent applications so not provide support the claimed limitations of the instant application.

Although Applicant's amendment filed 8/17/09 has rendered the filing date of instant claims 1, 24, 25, 33, 38 and 39 to be the filing date of the provisional parent application serial no. 60/352,284, *i.e.,* 1/30/02, for the purpose of prior art rejections, Applicant's arguments have been fully considered but are not persuasive as pertains to claims 21, 23, 34-36 and 40.

Applicant's arguments are of record on pages 17-19 of the said amendment. Applicant points to support for each of the claims under examination in the parent provisional application.

However, the said parent application does not provide support for the following limitations:

- of claim 21: "at a frequency of at least 10 per 10^4 PBLs" (the disclosure is to a frequency of 35 per 10^4 PBL for SEQ ID NO: 5)
- of claim 23: "chronic lymphatic leukemia and chronic myeloid leukemia" (the disclosure is to the genus of leukemia)
- of claim 34: "chronic lymphatic leukemia and chronic myeloid leukemia" (the disclosure is to the genus of leukemia)
- of claim 35: "where the composition elicits the production in a recipient subject of effector T-cells having a cytotoxic effect against the cancer cells" (the disclosure is to detection of TIL that are already present in the patient that are not elicited by administration of a composition comprising the peptide)
- of claim 36: "or in tumor tissue" (disclosure is to PBLs)
- of claim 40: "which is multimeric" (disclosure is to a complex of the peptide and of Class I HLA or a fragment thereof)

17. Applicant's amendment filed 8/17/09 has overcome the prior rejection of claims 1, 24, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) as evidenced by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

18. Applicant's amendment filed 8/17/09 has overcome the prior rejection of claims 1, 24, 38 and 39 under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

19. It is noted by the Examiner that Inventor Mads Hald Andersen had filed a Katz-type declaration under 37 C.F.R. 1.132 on 9/24/07 with regard to the two above-mentioned Andersen *et al* references. Consequently, no 102(a) rejections are being made over instant claims 1, 24, 38 and 39 based upon the said references.

20. Applicant's amendment filed 8/17/09 has overcome the prior rejection of claims 1, 24, 25, 28 and 33 under 35 U.S.C. 102(b) as being anticipated by WO 02/072631 A2 (9/19/02).

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 21, 23, 36 and 40 stand rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) as evidenced by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

It is noted by the Examiner that the publication date listed on the Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference), *i.e.,* 2/2000, is a print error on the part of the publisher. The said reference is published in volume 61, publication date 2/2001.

Andersen *et al* teach the human survivin peptide with the sequence LMLGEFLKL (1 uM, substitution analog peptide), that corresponds to SEQ ID NO: 5 of the instant claims. Andersen *et al* further teach that this peptide has a *C50* (uM) value of 1 uM as determined in an assembly assay for peptide binding to HLA-A2.1 molecules. Andersen *et al* teach that a CLL cancer patient's IFN-γ producing PBL responded strongly against the analog peptide LMLGEFLKL at 35 per 10^4 cells in an ELISPOT assay (see entire reference, especially Table 1 and Results).

Evidentiary reference Andersen *et al* (2001) teach the human survivin substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* could exhibit cytotoxicity against the) HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3 (see entire reference, especially results).

Claim 40 is included in this rejection because the art reference teaches complexes of the survivin HLA-A2-binding peptides with HLA-A2.1, and wherein the HLA/peptide complexes are contacting a T cell, they are multimeric. The instant claims do not recite wherein the complex is isolated.

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable

weight *per se*, and the claims read on the active or essential ingredients of the composition.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record on page 20 of the amendment filed 8/17/09.

Applicant argues that the amended claims find full support in the provisional application as originally filed and that the declaration of Dr. Andersen under 37 C.F.R. 1.132 establishes that the Andersen *et al* articles are describing Applicant's own work.

However, the instant claims do not have support in the parent provisional application 60/352,284 as enunciated supra in this Office Action, and the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration.

23. Claims 21, 23, 36 and 40 stand rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

Andersen *et al* teach the peptide LMLGEFLKL (human servivin substitution analog peptide, SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.*, exhibit cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach the survivin LTLGEFLKL nonamer peptide (see entire reference, especially results).

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.*, were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record on page 20 of the amendment filed 8/17/09. Applicant argues that the amended claims find full support in the provisional application as originally filed and that the declaration of Dr. Andersen under 37 C.F.R. 1.132 establishes that the Andersen *et al* articles are describing Applicant's own work.

However, the instant claims do not have support in the parent provisional application 60/352,284 as enunciated supra in this Office Action, and the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration.

24. Claims 21, 23, 34-36 and 40 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/072631 A2 (9/19/02).

WO 02/072631 A2 teaches a peptide with the sequence LMLGEFLKL, the sur1M2 peptide analog that binds to HLA-A2.1, which peptide sequence is identical to SEQ ID NO: 5 of the instant claims, and use of the peptide for detection of T cells specific for the complex formed by HLA-A2.1 and the said peptide. WO 02/072631 A2 further teaches complexes of this peptide with HLA-A2 and including in the form of a therapeutic composition (especially abstract, Example 1 at page 159, claims 1-42, page 155 at the first paragraph, and claim 82).

With regard to the inclusion of claims 34-36, the art reference teaches combining the isolated peptide with the MHC and β2m to produce MHC/peptide complexes.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record on pages 20-21 of the amendment filed 8/17/09.

Applicant argues that the amended claims find full support in the provisional application as originally filed.

However, the instant claims do not have support in the parent provisional application 60/352,284 as enunciated supra in this Office Action.

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. Claims 21, 23, 34-36 and 40 stand rejected under 35 U.S.C. 103(a) as being obvious over Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) in view of U.S. Patent No. 6,572,864 (of record).

Andersen *et al* teach the human servivin peptide LMLGEFLKL (substitution analog peptide, SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide

complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.*, exhibit cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach the survivin LTLGEFLKL nonamer peptide. Andersen *et al* teach combining a survivin based immunotherapy with conventional cancer chemotherapy to ascertain if the combination may prove to be an effective modus operandi to fight cancer (see entire reference, especially results).

Andersen *et al* do not teach wherein the peptide is comprised in an immunogenic composition.

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes or analogs thereof in a suitable diluent such as saline or water or adjuvants for use in a pharmaceutical composition.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide taught by Andersen *et al* in a composition along with a pharmaceutically acceptable carrier as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to test the peptide *in vivo* for immunogenicity and possible treatment efficacy.

With regard to the limitation, "immunogenic" the claimed composition appears to be similar to the composition of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's arguments are of record in the amendment filed 8/17/09 on page 21.

Applicant argues that the amended claims find full support in the provisional application as originally filed and that the declaration of Dr. Andersen under 37 C.F.R. 1.132 establishes that the Andersen *et al* articles are describing Applicant's own work.

However, the instant claims do not have support in the parent provisional application 60/352,284 as enunciated supra in this Office Action, and the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration.

27. Claims 21, 23, 34-36 and 40 stand rejected under 35 U.S.C. 103(a) as being obvious over Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) in view of U.S. Patent No. 6,572,864 (of record).

It is noted by the Examiner that the publication date listed on the Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference), *i.e.,* 2/2000, is a print error on the part of the publisher. The said reference is published in volume 61, publication date 2/2001.

Andersen *et al* teach the human survivin peptide with the sequence LMLGEFLKL (1 uM, substitution analog peptide), that corresponds to SEQ ID NO: 5 of the instant claims. Andersen *et al* further teach that this peptide has a *C50* (uM) value of 1 uM as determined in an assembly assay for peptide binding to HLA-A2.1 molecules. Andersen *et al* teach that a CLL cancer patient's IFN-γ producing PBL responded strongly against the analog peptide LMLGEFLKL at 35 per 10^4 cells in an ELISPOT assay. Andersen *et al* teach that survivin may serve as a widespread target for therapeutic CTL responses for anticancer immunotherapeutic strategies (see entire reference, especially Table 1 and Results).

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes or analogs thereof in a suitable diluent such as saline or water or adjuvants for use in a pharmaceutical composition.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide taught by Andersen *et al* in a composition along with a pharmaceutically acceptable carrier as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to test the peptide *in vivo* for immunogenicity and possible treatment efficacy.

With regard to the limitation, "immunogenic" the claimed composition appears to be similar to the composition of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's arguments are of record in the amendment filed 8/17/09 on pages 21-22.

Applicant argues that the amended claims find full support in the provisional application as originally filed and that the declaration of Dr. Andersen under 37 C.F.R. 1.132 establishes that the Andersen *et al* articles are describing Applicant's own work.

However, the instant claims do not have support in the parent provisional application 60/352,284 as enunciated supra in this Office Action, and the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration.

28. Applicant's Terminal Disclaimer filed 8/17/09 has overcome the prior rejection of record of claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-7, 14, 17-24, 26-34, 44 of copending Application No. 10/354,090 in view of Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) or Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) or WO 02/072631 A2.

29. Applicant's Terminal Disclaimer filed 8/17/09 has overcome the prior rejection of record of claims 1, 21, 23-25, 28, 33-36 and 50 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9, 11, 12, 14-16, 27-37 and 44 of copending Application No. 10/543,755.

30. Applicant's Terminal Disclaimer filed 8/17/09 has overcome the prior rejection of record of claims 38-40 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9, 11, 12, 14-16, 27-37 and 44 of copending Application No. 10/543,755 in view of WO 02/072631 A2.

31. Claim 24 is objected to because of the following informality: Claim 24 does not recite the ATCC number for cell line MCF-7. Appropriate correction is required.

32. Claims 1 and 25 are free of the art of record.

33. The references 3 and 4 crossed-out in Applicant's Form 1449 filed 10/23/09 have not been considered because they are not complete citations, *i.e.,* are missing the author name.

34. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

35. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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